THE ROLE OF PET-CT IMAGING IN PROSTATE CANCER

AUTHORS

1. Manil Subesinghe[1,2] MBBS BSc MRCP FRCR
2. Meghana Kulkarni[2] MBBS BSc MRCS
3. Gary J Cook[1,2] MBBS MSc MD FRCP FRCR

AFFILIATIONS

[1]King's College London & Guy's & St. Thomas' PET Centre, St. Thomas' Hospital, London, UK

[2]Department of Cancer Imaging, School of Biomedical Engineering and Imaging Sciences, King's College London, London, UK

CORRESPONDING AUTHOR

Manil Subesinghe

King's College London & Guy's and St. Thomas' PET Centre, 1st Floor Lambeth Wing, St. Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH

Email: manil.subesinghe@kcl.ac.uk

ABSTRACT

Prostate cancer (CaP) is the commonest malignancy to affect in men in the UK. Extraprostatic disease detection at staging and in the setting of biochemical recurrence (BCR) is essential in determining treatment strategy. Conventional imaging including computed tomography (CT) and bone scintigraphy (BS) are limited in their ability to detect sites of loco-regional nodal and metastatic bone disease, particularly at clinically relevant low prostate specific antigen (PSA) levels. The use of positron emission tomography-computed tomography (PET-CT) has helped overcome these deficiencies and is leading a paradigm shift in the management of CaP using a wide range of radiopharmaceuticals. Their

mechanisms of action, utility in both staging and BCR, and comparative strengths and weaknesses will be covered in this article.

KEYWORDS

Positron emission tomography computed tomography

Prostatic neoplasms

Neoplasm staging

Recurrence

Prostate-specific antigen

ABBREVIATIONS

BCR = biochemical recurrence

BPH = benign prostatic hyperplasia

BS = bone scintigraphy

CaP = prostate cancer

CT = computed tomography

DCE = dynamic contrast enhanced

DR = detection rate

DW = diffusion weighted

EMA = European Medicines Agency

FCH = [^{18}F]fluoromethylcholine

FDA = Food and Drug Administration

FEC = [^{18}F]fluoroethylcholine

GS = Gleason Score

MIP = maximum intensity projection

mpMRI = multiparametric magnetic resonance imaging

NICE = National Institute for Health Care and Excellence

PET = positron emission tomography

p.i = post-injection

PIRADS = Prostate Imaging Reporting and Data System

PSA = prostate specific antigen

PSAdt = PSA doubling time

PSAvel = PSA velocity

PSMA = prostate specific membrane antigen

rhPSMA = radiohybrid PSMA

RP = radical prostatectomy

RT = radiotherapy

SPECT = single photon emission computed tomography

SUV_{max} = maximum standardised uptake value

ACKNOWLEDGEMENTS

The authors would like to thank Professor Antony Gee for proofreading the manuscript prior to submission. They authors also acknowledge financial support from the King's College London/University College London Comprehensive Cancer Imaging Centres funded by Cancer Research UK and Engineering and Physical Sciences Research Council in association with the Medical Research Council and the Department of Health (C1519/A16463), the Wellcome Trust EPSRC Centre for Medical Engineering at King's College London (WT203148/Z/16/Z), and UK Research & Innovation London Medical Imaging and Artificial Intelligence Centre.

Word count: 4847 words

INTRODUCTION

Prostate cancer (CaP) is the commonest cancer in men, with nearly 43,000 cases diagnosed in England and Wales in 2017-18[1]. Since the mid-1990s, incidence has risen by over 40%, due to an ageing population and increased detection, e.g. prostate specific antigen (PSA) testing, but has been accompanied by improved survival, due to earlier detection of low-risk slow growing cancers and more effective treatments. However, mortality rates remain static in several age groups, and have overall increased by 20% since the 1970s, reflecting ongoing mortality associated with high-risk aggressive CaP[2].

Extraprostatic disease detection is paramount in deciding the most appropriate treatment strategy. Despite the excellence of multiparametric magnetic resonance imaging (mpMRI), which includes diffusion weighted (DW) and dynamic contrast enhanced (DCE) imaging, for local staging[3], the sensitivity of conventional MRI[4,5] and computed tomography (CT)[5], for loco-regional nodal disease detection is limited, due to the inadequacy of size thresholds (8-10mm short axis diameter) to detect disease in otherwise normal appearing nodes, whilst bone scintigraphy (BS), the historic mainstay of metastatic bone disease assessment, has a diagnostic yield highly dependent on PSA level with poor exclusion for metastatic disease especially at low PSA levels[6,7].

Imaging research has focused on developing positron emission tomography (PET) radiopharmaceuticals that address these deficiencies. This article covers the common PET radiopharmaceuticals available for the simultaneous assessment of local, nodal, and distant disease, their mechanisms of action, use in both staging and biochemical recurrence (BCR), and comparative strengths and weaknesses. The use of 2-deoxy-2[^{18}F]fluoro-D-glucose PET-CT, which is of limited benefit in hormone sensitive CaP, but is helping guide evolving therapeutic strategies using molecular

radiotherapy for advanced aggressive metastatic castrate resistant CaP, is beyond the scope of this article but is discussed in detail in a recent review by Siva et al[8].

PET RADIOPHARMACEUTICALS

Radiolabelled choline analogues

Choline enters cells via cell surface transporters, and is phosphorylated by choline kinase into phosphocholine, a precursor of phosphatidylcholine, the major phospholipid component of cell membranes[9]. Radiolabelled choline uptake in CaP cells reflects increased expression of cell surface choline transporters[10] and upregulation of choline kinase activity[11] but not increased cellular proliferation or cell membrane synthesis per se[11,12].

The major advantages of [^{11}C]choline include minimal urinary excretion, allowing accurate assessment of the prostate bed and pelvic nodal basins, and early post-injection (p.i) imaging (5-15 minutes)[13] but its major drawback is its short half-life (20 minutes), limiting use to institutions with cyclotrons. The choline-inspired radiopharmaceuticals, [^{18}F]fluoromethylcholine (FCH) and [^{18}F]fluoroethylcholine (FEC), were developed to take advantage of the longer half-life of [^{18}F] (110 minutes), and permit more widespread availability. Despite high urinary excretion, and potential to hinder assessment of the pelvis, FCH/FEC have a higher positive detection rate (DR) than [^{11}C]choline[14], whilst FCH may have a higher diagnostic performance than FEC[15].

A traditional FEC/FCH imaging protocol comprises early dynamic and delayed (90 minutes p.i) pelvic imaging with half body imaging at 60 minutes p.i; the pelvic acquisitions help differentiate pathological prostatic uptake from physiological urinary activity and help characterise the nature of pelvic nodes; these acquisitions can however be safely omitted without adverse effect on accuracy[16]. Physiological uptake is observed in the salivary glands, liver, kidneys, pancreas, spleen, bone marrow and bowel

with low-grade uptake frequently observed in reactive nodes in the groins, axillae and chest (**Figure 1**). A recommended injected activity of 4 MBq/kg up to 370 MBq results in a maximum effective dose of 6.4 mSv[17].

[^{18}F]Fluciclovine

[^{18}F]Fluciclovine or [^{18}F]FACBC, is a radiolabelled synthetic amino acid analogue, initially developed to image brain tumours[18] whose utility in CaP was incidentally discovered during a study of renal carcinomas[19]. [^{18}F]Fluciclovine uptake reflects increased expression of amino acid transporters on CaP cell membranes[20] with L-type amino acid transporter 1 expression associated with high Gleason Score (GS) aggressive CaP[21].

Half-body imaging performed at 3-5 minutes p.i ensures high tumour-background ratios and minimises tumoural washout of radiopharmaceutical. [^{18}F]Fluciclovine has low urinary excretion, improving the ability to detect intraprostatic disease, although in 5-10% of cases, bladder activity may hinder assessment[22]. Elsewhere, there is intense physiological uptake in the liver and pancreas, moderate bone marrow uptake, moderate salivary and pituitary gland uptake, variable bowel uptake, and mild muscle activity, which increases with time[22] (**Figure 2**). A standard administered activity of 370 MBq results in an effective dose of 5.2 mSv[23].

Prostate Specific Membrane Antigen (PSMA)

PSMA is a transmembrane glycoprotein, with intracellular, transmembrane and extracellular components. PSMA is expressed on endothelial cells within the neovasculature of both normal proliferative tissues[24] and tumours including renal cell, transitional cell and colonic carcinomas[25], whilst in the central nervous system, it is expressed on astrocytes and known as glutamate carboxylase II[26]. In the prostate, PSMA is expressed on the prostatic epithelium and in the majority of prostatic

adenocarcinomas[25,27,28], with PSMA expression greatest and most homogeneous in high grade tumours, heterogeneous and patchy in low-indeterminate grade tumours, and both significantly greater than in benign prostatic epithelium[27,28].

Initial PSMA imaging used the radiolabelled monoclonal antibody [^{111}In]Capromab Pendetide (ProstaScint®), to target the intracellular component of PSMA, which is only accessible through cell membrane destruction (necrosis or apoptosis), i.e. non-viable cells[29]. Images were hindered by poor tumour penetration and high background activity with resultant suboptimal detection of pelvic nodal disease in staging[30]. Consequently, PSMA PET radiopharmaceutical development focused on small urea based PSMA ligands (inhibitors), which target the extracellular active substrate recognition site of PSMA with high binding affinity, and are internalised and retained within CaP cells, thereby exhibiting rapid plasma clearance and high tumour-background ratios[31].

^{68}Ga-labelled PSMA radiopharmaceuticals

[^{68}Ga]Ga-PSMA-11 or [^{68}Ga]Ga-PSMA-HBED-CC, first described in 2012[32], is the most studied and utilised PSMA PET radiopharmaceutical. There is intense physiological uptake in the lacrimal and salivary glands, with slightly lower intensity uptake in the liver, spleen, bowel, and sympathetic ganglia, e.g. coeliac and cervical ganglia[33], and minimal uptake in normal prostatic tissue and in bone marrow (**Figure 3**). [^{68}Ga]Ga-PSMA-11 is predominantly renally excreted with intense activity in the urinary tract; focal ureteric activity can be mistaken for pathological nodal uptake or potentially obscure uptake in adjacent nodes, whilst bladder activity can hamper prostate bed assessment.

Half body imaging is usually performed 60 minutes p.i[34], although delayed time point imaging at 180 minutes p.i increases uptake, contrast and DR, through clarification of equivocal lesions[35,36]. A modified protocol with imaging at 90 minutes p.i preceded by 1 litre pre-hydration and furosemide

induced diuresis improves tumour contrast with the potential to increase DR[37]. A recommended injected activity between 1.8-2.2 MBq/kg up to a maximum of 200 MBq results in a maximum effective dose of 4.6 mSv[38].

[^{68}Ga]Ga-PSMA-617[39] and [^{68}Ga]Ga-PSMA-I&T[40] are alternative PSMA PET radiopharmaceuticals with similar imaging characteristics to [^{68}Ga]Ga-PSMA-11 but with superior theranostic capabilities. At our institution, we use [^{68}Ga]Ga-THP-PSMA, which offers rapid, room temperature, one-step kit based radiolabelling, similar to established techniques used for ^{99m}Tc-labelled radiopharmaceuticals[41]. It has lower physiological uptake in the salivary glands, liver, and spleen, in comparison with [^{68}Ga]Ga-PSMA-11 and [^{68}Ga]Ga-PSMA-I&T, but with earlier renal excretion and higher urinary activity[42,43]; we routinely perform early dynamic pelvic imaging (0-10 minutes) to overcome this (**Figure 4**). Tracer uptake in malignant lesions, measured using maximum standardised uptake values (SUV_{max}), is significantly with lower with [^{68}Ga]Ga-THP-PSMA compared with [^{68}Ga]Ga-PSMA-11 (SUV_{max} 10.7 vs. SUV_{max} 30.3)[42] and [^{68}Ga]Ga-PSMA-I&T (SUV_{max} 7.5 vs SUV_{max} 21.3)[43], but with similar tumour-background ratios. A maximum administered activity of 200 MBq results in an effective dose of 4.1 mSv.

^{18}F-labelled PSMA radiopharmaceuticals

Despite the success of ^{68}Ga-labelled PSMA radiopharmaceuticals, disadvantages include; ^{68}Ge/^{68}Ga generator purchase costs; limited number of doses per generator elution, requiring several productions per day and/or purchasing of additional generators to meet demand; and relatively short physical half-life of ^{68}Ga (68 minutes), which invariably limits ^{68}Ga-labelled PSMA PET-CT examinations to centres with ^{68}Ge/^{68}Ga generators[44]. Research has focused on developing cyclotron produced ^{18}F-labelled PSMA PET radiopharmaceuticals, to allow a greater number of examinations due to higher amounts of available radioactivity from a cyclotron, wider availability due to the longer physical half-

life of ^{18}F, and improved spatial resolution and image quality, due to its lower positron energy and range.

[^{18}F]DCFBC, the first ^{18}F-labelled PSMA PET radiopharmaceutical, was limited by high blood pool activity hindering assessment of the pelvic nodal basins[45]. A second generation ^{18}F-labelled PSMA PET radiopharmaceutical, [^{18}F]DCFPyL, demonstrated very low blood pool activity and markedly higher uptake in malignant lesions compared to [^{18}F]DCFBC[46]. Delayed time point imaging at 120 minutes p.i increases tumoural uptake, which can result in more detected lesions and a change in TNM staging[47]. A maximum administered activity of 370 MBq results in an effective dose of 6.1 mSv[46].

[^{18}F]PSMA-1007, a more recently developed ^{18}F-labelled PSMA PET radiopharmaceutical structurally related to PSMA-617, includes a chelator capable of binding therapeutic radionuclides. Its biodistribution is similar to other PSMA PET radiopharmaceuticals except for its minimal urinary clearance, due to its predominant hepatobiliary excretion and renal retention (**Figure 5**), which is advantageous for assessment of the pelvis[48]. Delayed imaging at 120 minutes p.i shows a significant increase in tumoural uptake with very low urinary activity in the bladder that reduces with time[49]. An injected activity between 200-250 MBq results in an effective dose between 4.4-5.5 mSv[48].

STAGING

mpMRI is the imaging modality of choice for patients with clinically suspected localised CaP with good diagnostic accuracy for cancer detection and extracapsular extension using the Prostate Imaging Reporting and Data System (PIRADS)[3]. In biopsy naïve patients, foci of clinically significant disease (PIRADS ≥3) are targeted with percutaneous biopsies, a strategy superior to systematic non-targeted biopsies[50], to obtain histological confirmation and help risk stratify patients using the GS, mpMRI findings and PSA level[51]. Assessment for extraprostatic disease is vital prior to embarking upon curative intent radical prostatectomy (RP) or radiotherapy (RT) with current guidelines[52] recommending abdomino-pelvic CT and BS in patients with intermediate and high-risk CaP; PET-CT is challenging this status quo.

Radiolabelled choline analogues

Radiolabelled choline PET/PET-CT is superior to conventional imaging for extraprostatic disease detection[53] but has limited accuracy in differentiating between benign and malignant intraprostatic pathologies[54]. Prospective studies evaluating the use of FCH PET-CT in patients with intermediate and high-risk CaP, have reported suboptimal sensitivities (45-73.2%) but high specificities (87.6-96%) for nodal disease[55,56]; sensitivity is improved for nodes ≥ 5mm in diameter[55] but false positive nodal uptake remains problematic[56] (**Figure 6**). These studies reported unexpected findings of metastatic bone disease, some in patients without histological evidence of nodal disease, with Beheshti et al. reporting a 15% (19/130 patients) change from surgical to non-surgical management[55]. A meta-analysis of 10 radiolabelled choline PET/PET-CT studies (441 patients) confirmed suboptimal pooled sensitivity (49%) but high specificity (95%) for nodal disease along with a higher sensitivity associated with [^{11}C]choline compared with FCH/FEC[57].

[^{18}F]Fluciclovine

There is a paucity of literature regarding [^{18}F]Fluciclovine PET-CT use in staging of CaP. Small prospective single centre studies have confirmed higher uptake in tumoural foci compared to normal prostate, but not dissimilar to uptake in benign prostatic hyperplasia (BPH), thereby limiting specificity[58,59]. In addition, Jambor et al.[59] reported that only 1 out of 7 patients with proven metastatic nodal disease were identified on pre-operative imaging with undetected nodes ≤ 7mm in maximum dimension[59]. A multi-centre trial of 68 patients with CaP (42 patients awaiting RP) reported that none of the 7 RP patients with histologically proven nodal disease demonstrated [^{18}F]Fluciclovine uptake with the largest node ≤ 5mm in maximum dimension[60]; this reflects a combination of insufficient tumour burden in nodes to generate a detectable PET signal coupled with limitations of PET spatial resolution. A meta-analysis confirmed a pooled sensitivity of 87% and specificity of 84% for primary tumour detection, and pooled sensitivity of 56% and specificity of 98% for nodal staging[61] (**Figure 7**).

^{68}Ga-labelled PSMA radiopharmaceuticals

A handful of studies have confirmed the superiority of ^{68}Ga-labelled PSMA PET-CT over conventional imaging CaP staging[62]. A recent small prospective study of 20 patients undergoing extended lymph node dissection prior to RT, reported a ^{68}Ga-labelled PSMA PET-CT sensitivity of 39% for loco-regional nodal disease, compared with 8% for conventional MRI/CT[63], whilst a prospective study of 113 patients confirmed significantly higher sensitivity (96.2% vs 73.1%) and accuracy (99.1 vs 84.1%) using ^{68}Ga-labelled PSMA PET-CT compared with BS for metastatic bone disease, particularly in relation to lytic and marrow metastases[64] (**Figure 8**).

Several studies have assessed the diagnostic performance of ^{68}Ga-labelled PSMA PET-CT for nodal staging using histopathological validation. The largest series of 208 patients reported a per patient

sensitivity for nodal disease of 38.2% (21/55 patients) and per node sensitivity of 24.4% (42/172 nodes); the median diameter of malignant nodes was 4.8mm (range 0.2-40mm) with < 15% of histologically proven malignant nodes measuring < 5mm in maximum diameter identified pre-operatively[65]. A recent literature review identified 2 prospective studies (63 patients) with per patient sensitivities of 64-100%, per node sensitivities of 50-58%, and high specificities of 90-95%, and 9 retrospective studies (696 patients) with per patient sensitivities of 33-100%, per node sensitivities of 24.4-96%, and high specificities of 80-100%[66]. Koschel et al. in their review identified 5 meta-analyses, each including between 4-6 eligible studies, with reported pooled sensitivities of 61-80% and pooled specificities of 95-99% for nodal disease[67].

Despite its moderate sensitivity, ^{68}Ga-labelled PSMA PET-CT has been shown to have a significant impact on management, with a 21% change in management intent in a multi-centre prospective Australian study using [^{68}Ga]Ga-PSMA-11 PET-CT[68] and a 24% management change in a recent study from our institution using [^{68}Ga]Ga-THP-PSMA PET-CT[69] (**Figure 9**). Results are eagerly awaited from the recently completed ProPSMA study, an Australian multi-centre prospective randomised control trial involving 300 patients with newly diagnosed CaP, which compares ^{68}Ga-labelled PSMA PET-CT with conventional imaging and BS. Results will provide robust evidence regarding the diagnostic accuracy of ^{68}Ga-labelled PSMA PET-CT, its incremental benefit over conventional imaging and resultant clinical impact, as well as important cost and outcome data[70].

^{18}F-labelled PSMA radiopharmaceuticals

There is limited evidence regarding the use of ^{18}F-labelled PSMA PET-CT in CaP staging. Initial studies using [^{18}F]DCFBC PET-CT confirmed its ability to differentiate intraprostatic tumour from BPH and normal prostate tissue but with inferior sensitivity to mpMRI[71,72]; there are no data regarding its efficacy for nodal disease detection. A preliminary study of 10 patients undergoing [^{18}F]PSMA 1007

PET-CT, reported intense uptake in all primary tumours, and excellent sensitivity (94%) for nodal disease, with 18/19 histologically proven lymph node metastases detected pre-operatively with a median nodal diameter of 5mm (range 1-18mm)[48] (**Figure 10**). The only available prospective single centre phase II study assessing [^{18}F]DCFPyL PET-CT in 25 patients, reported that all patients demonstrated focal increased prostatic uptake, the sensitivity and specificity for nodal disease was 71.4% and 89%, respectively with 50% of involved nodes < 3mm in size, and 3 patients (12%) had unsuspected distant nodal metastatic disease[73].

COMPARATIVE STUDIES WITH PSMA PET RADIOPHARMACEUTICALS IN PRIMARY STAGING

There are few comparative studies between PET radiopharmaceuticals in staging of CaP. A retrospective subgroup analysis of 20 patients who underwent both [^{68}Ga]Ga-PSMA-11 PET-CT and [^{11}C]choline PET-CT, found concordance in prostatic tumoural uptake but a greater number of involved nodes and bone metastases with [^{68}Ga]Ga-PSMA-11[74]. A prospective study between [^{18}F]PSMA-1007 PET-CT and [^{68}Ga]Ga-PSMA-11 PET-CT in 16 patients showed comparable ability to detect the dominant prostatic tumoural focus, although the absence of histologically proven nodal disease prevented further comparisons. A comparative study between [^{18}F]PSMA-1007 PET-CT and [^{18}F]DCFPyL PET-CT in 12 patients showed equivalence for imaging local, nodal and distant metastatic disease[75].

BCR

Following RP or RT, 27-53% of patients develop BCR, which is defined as a rising PSA without corroborative histological or imaging evidence of disease relapse[52]; the PSA level that defines BCR depends on the primary treatment. Post-RP, after which PSA levels should reach undetectable levels within 4 weeks, a PSA level of ≥ 0.4 ng/ml, followed by further increase, is the best predictor of metastatic disease progression, although 2 or more successive PSA rises ≥ 0.2 ng/ml is an acceptable alternative definition[76]. Following RT, the definition of treatment failure, is any PSA increase ≥ 2.0 ng/ml higher than the PSA nadir value, regardless of the nadir value[77].

BCR does not indicate inevitable progression to clinically significant disease and/or CaP related mortality. In a cohort of nearly 2000 post-RP patients, 304 (15%) patients developed BCR, with only 103 of those patients (34%) developing metastatic disease within the 15-year follow-up period, with a median of 8 years from BCR to the development of detectable metastatic disease[78]. Despite this, with appropriate risk stratification and identification of high-risk features[79], early salvage treatment, in particular salvage RT at low PSA levels can improve outcome[80].

Radiolabelled choline analogues

Radiolabelled choline PET/PET-CT is superior to conventional imaging in BCR[81,82] with several meta-analyses confirming high diagnostic accuracy[83-85]; a meta-analysis of [^{11}C]choline PET/PET-CT studies reported an overall DR of 62% with pooled sensitivity and specificity of 89% for any site relapse[83] (**Figure 11**). The DR and sensitivity of radiolabelled choline PET-CT is dependent on PSA level and PSA kinetics, i.e. PSA doubling time (PSAdt) and PSA velocity (PSAvel)[86]. A systematic review of the role of imaging in early recurrent CaP reported pooled DRs for [^{11}C]choline PET/PET-CT of 0-31.3% at PSA levels < 0.5 ng/ml, and 14.3-44.1% at PSA levels < 1.0 ng/ml, which were slightly better with FCH/FEC PET/PET-CT (8.3-28.1% PSA < 0.5 ng/ml, 16.7-76.0% PSA < 1.0 ng/ml)[87]. A meta-analysis of

radiolabelled choline PET-CT studies reported a pooled DR of 58% with a significant rise in DR to 65% if the PSAdt was ≤ 6 months, and up to 71% and 77% if the PSAvel was > 1.0 or > 2.0 ng/ml/year, respectively[88].

This superiority of radiolabelled choline PET/PET-CT over conventional imaging in BCR translates into changes in clinical management. A prospective multi-centre trial assessing the impact of FCH PET-CT in 179 patients with prior negative/equivocal conventional imaging, reported a 56% change in management[89]. A 150 patient retrospective study assessing the impact of [^{11}C]choline PET-CT reported a slightly lower overall clinical impact of 46.7% (70/150 patients), with 38.6% (27/70) of decisions classed as a major change in management (switch from salvage to palliative therapy or vice versa) and 61.4% (43/70) as minor (same therapeutic category but with adjustment)[90] (**Figure 12**). Although incorporated into early iterations of international CaP guidelines[52], radiolabelled choline PET-CT in BCR is being replaced by more novel PET radiopharmaceuticals, as discussed later.

[^{18}F]Fluciclovine

[^{18}F]Fluciclovine PET-CT is superior to ProstaScint® single photon emission computed tomography (SPECT)-CT[91], contrast-enhanced CT[92] and [^{11}C]choline PET-CT[93] in BCR with meta-analyses confirming pooled sensitivities of 79-87% and specificities of 66-69%[61,94], although DRs at different PSA levels are not reported. Higher DRs at higher PSA levels have been observed in smaller studies and confirmed in larger prospective trials (**Figure 13**). The multicentre retrospective BED-001 study of 596 patients[95], reported an overall DR of 67.7% (median PSA 2.0 ng/ml, range 0.05-82.0 ng/ml) and a 41% DR at a PSA level ≤ 0.79 ng/ml. The US multi-centre prospective LOCATE study of 213 patients reported an overall DR of 57% (median PSA 1.0 ng/ml, range 0.2-93.5 ng/ml), DRs of 31%, 50%, 66% and 84% at PSA levels of < 0.5 ng/ml, 0.5-1.0 ng/ml, 1.0-2.0 ng/ml, and > 2.0 ng/ml, respectively, and was associated with a 59% (126/213 patients) change in management, of which 78% (98/126) were

'major', i.e. change in treatment modality[96]. The smaller UK multi-centre prospective FALCON study of 104 patients, reported an overall DR of 56% (median PSA 0.79 ng/ml, range 0.04-28.0 ng/ml), DRs of 33% and 93% at PSA levels of ≤ 1.0 ng/ml, and > 2.0 ng/ml, respectively, and an was associated with a 63% change in management (66/104) of which 65% (43/66) of decisions were major[97]. [^{18}F]Fluciclovine was approved by the U.S Food and Drug Administration (FDA) for recurrence detection in CaP in May 2016, received marketing authorisation by the European Medicines Agency (EMA) in May 2017, and is pending approval by the National Institute for Health Care and Excellence (NICE).

^{68}Ga-labelled PSMA radiopharmaceuticals

^{68}Ga-labelled PSMA PET-CT is superior to conventional imaging[98-100] and other available PET radiopharmaceuticals in BCR, particularly at low PSA levels with DRs between 11.3-58.3% at PSA levels < 0.2 ng/ml, and 11.0-65.0% at PSA levels < 0.5 ng/ml[87]. Perera et al.[101] in a 2019 meta-analysis reported impressive pooled DRs at low PSA levels (33% PSA < 0.2 ng/ml, 45% PSA 0.2-0.5 ng/ml), similar to results by Hope et al., which only incorporated studies with histological validation, with pooled sensitivity of 99%, specificity of 76% and a 40% DR at a PSA < 0.2 ng/ml[102]. Although a recent meta-analysis demonstrated an increase DR with shorter doubling times (60% PSAdt > 6 months, 83% in patients with a PSAdt < 6 months)[103], this was not statistically significant and there remains no clear correlation between PSA kinetics and ^{68}Ga-labelled PSMA PET-CT DR in BCR.

Large prospective trials published since these meta-analyses have shown similar results. A multi-centre prospective trial of 635 patients reported an overall DR of 75% (median PSA 2.1 ng/ml, range 0.1-1154 ng/ml), which increased with PSA level (38% PSA < 0.5 ng/ml, 57% PSA 0.5-1.0 ng/ml, 84% PSA 1.0-2.0 ng/ml)[104], whilst a single centre prospective trial of 314 patients reported an overall DR of 62.7% (median PSA 0.83 ng/ml, range 0.003-80 ng/ml), which also increased with PSA level (27.3%

PSA < 0.2ng/ml, 47.1% PSA 0.2-1.0 ng/l, 75% PSA 1.0-2.0 ng/ml)[105]; both studies failed to demonstrate a significant correlation between DR and PSAdt.

High DRs at such low PSA levels result in significant changes in management. A review of 12 ^{68}Ga-labelled PSMA PET-CT studies (1346 patients) reported management change ranging between 30.2-76.0%[106]; amongst 60% of patients, the main changes were avoidance of systemic therapy and new indication for PET-directed therapy, which included prostate/pelvic bed RT or treatment of oligometastatic disease (**Figure 14**).

The majority of evidence for ^{68}Ga-labelled PSMA PET-CT in BCR revolves around [^{68}Ga]Ga-PSMA-11, but other ^{68}Ga-labelled PSMA ligands including [^{68}Ga]Ga-PSMA-IT&T[107] and [^{68}Ga]Ga-THP-PSMA[69,108] have been assessed. A retrospective analysis of 99 patients post-RP undergoing [^{68}Ga]Ga-THP-PSMA PET-CT reported an overall DR of 52.5% (mean PSA 94.1 ng/ml, range 0.01-8400 ng/ml), with DRs of 22.2%, 20%, 14.3% and 54.5% at PSA levels of < 0.2 ng/ml, 0.2-0.5 ng/ml, 0.5-1.0 ng/ml and 1.0-2.0 ng/ml, which are lower than with other PSMA PET radiopharmaceuticals[108]. Despite this, a recent study of 68 patients with BCR from our institution confirmed the clinical impact of [^{68}Ga]Ga-THP-PSMA PET-CT with a 34% (23/68) change in management with a similar overall DR of 59% (mean PSA 4.4 ng/ml, range 0.16-71.02 ng/ml)[69] (**Figure 15**).

^{18}F-labelled PSMA radiopharmaceuticals

Although the evidence base for ^{18}F-labelled PSMA PET-CT in BCR is relatively immature, a systematic review and meta-analysis of 6 studies (645 patients) reported an overall pooled DR of 81% and 49% DR at PSA levels ≤ 0.5 ng/ml[109]. A prospective study assessing [^{18}F]DCFBC PET-CT in 68 patients reported an overall DR of 60.3% (mean PSA 4.4 ng/ml, range 0.2-37.4 ng/ml), which increased with

PSA level (15% PSA < 0.5 ng/ml, 46% PSA 0.5-1.0 ng/l, 83% PSA 1.0-2.0 ng/ml) and was associated with a 51.2% management change, despite its known limitation of high blood pool activity[110].

A prospective study assessing [^{18}F]DCFPyL PET-CT in 130 patients[111], reported a higher overall DR of 84.6% (mean PSA 5.2 g/ml), higher DRs at low PSA levels (60% PSA 0.4-0.5 ng/ml, 78% PSA 0.5-1.0 ng/ml) and higher change in management (87.3%) compared to [^{18}F]DCFBC PET-CT[110]. A further prospective study assessing [^{18}F]DCFPyL PET-CT in 90 patients reported an overall DR of 77.8% (median PSA 2.5ng/ml, range 0.21-35.5 ng/ml) and broadly similar PSA specific DRs but found that in post-prostatectomy patients exclusively, PSA level, PSAdt and PSAvel correlated with PET-CT DRs[112].

A prospective study assessing [^{18}F]PSMA-1007 PET-CT in 40 patients with BCR with PSA levels ≤ 2.0 ng/ml reported an overall DR of 60% (median PSA 0.65 ng/ml), which was dependent on PSA level (39% PSA < 0.5 ng/ml, 55% PSA 0.5-1.0 ng/ml, 100% PSA 1.0-2.0 ng/ml)[113], whilst a larger retrospective analysis of 251 patients reported a higher overall DR of 81.3% (median PSA 1.2ng/ml, range 0.2-228 ng/ml) with DRs of 61.5%, 74.5%, 90.9% at PSA levels of 0.2-0.5 ng/ml, 0.5-1.0 ng/ml, 1.0-2.0 ng/ml[114], respectively; these are comparable, if not better than those published for other PSMA PET radiopharmaceuticals (**Figure 16**).

COMPARATIVE STUDIES WITH PSMA PET RADIOPHARMACEUTICALS IN BCR

^{68}Ga- and ^{18}F-labelled PSMA vs. radiolabelled choline

A prospective comparative study between [^{68}Ga]Ga-PSMA-11 PET-CT and FCH PET-CT in 38 patients reported a superior overall DR for [^{68}Ga]Ga-PSMA-11 compared to FCH (66% vs. 32%) across all PSA levels (mean 1.72 ng/ml, range 0.04-12.0 ng/ml) and most evident at low PSA levels, e.g. 50% vs. 12.5% PSA < 0.5 ng/ml[115]. A similar sized prospective study comparing [^{68}Ga]Ga-PSMA-11 PET-CT and [^{11}C]choline PET-CT reported similar findings[116]. The only available prospective head-to-head

comparison of [^{18}F]PSMA-1007 PET-CT and FCH PET-CT in 40 patients with BCR and PSA levels ≤ 2.0 ng/ml (median PSA 0.7 ng/ml), confirmed the superiority of [^{18}F]PSMA-1007 with a significantly higher DR and higher number of lesions detected per patient[117]. A meta-analysis of 5 head-to-head comparison studies between PSMA PET-CT and radiolabelled choline PET-CT, reported a higher overall DR (78% vs. 56%) and higher DR at PSA levels ≤ 1.0ng/ml (54% vs. 27%) for PSMA PET-CT[118].

^{68}Ga- and ^{18}F-labelled PSMA vs. [^{18}F]Fluciclovine

Calais et al. conducted a robustly designed prospective head-to-head comparison study between [^{68}Ga]Ga-PSMA-11 PET-CT and [^{18}F]Fluciclovine PET-CT in 50 patients (PSA ≤ 2.0 ng/ml) post-RP; 44/50 patients (88%) had a PSA level ≤ 1.0ng/ml[119]. Overall DRs were significantly higher with [^{68}Ga]Ga-PSMA-11 (56% vs. 26%) at all PSA levels (46% vs. 27% PSA 0.2-0.5 ng/ml, 67% vs. 28% PSA 0.5-1.0 ng/ml, 67% vs. 17% PSA 1.0-2.0 ng/ml), with tumour-background ratios for PET positive lesions 7 times higher with [^{68}Ga]Ga-PSMA-11 than with [^{18}F]Fluciclovine. Although DRs for prostate bed recurrence were similar, for sites of extraprostatic disease (nodal, skeletal and visceral), DRs were > 2 times higher with [^{68}Ga]Ga-PSMA-11. A similar sized prospective comparative study between [^{68}Ga]Ga-PSMA-11 PET-CT and [^{18}F]Fluciclovine PET-CT in 58 patients (post-RP or post-RT), reported no significant difference in overall DRs (82.8% vs. 79.3%). However, comparative DRs at clinically important low PSA levels, i.e. ≤ 2ng/ml were not reported, which is relevant given the heterogeneous patient cohort assessed and their widely varying PSA levels (median PSA 14.9 ng/ml, range 0.2-230 ng/ml) at the time of imaging[120].

^{68}Ga-labelled PSMA vs. ^{18}F-labelled PSMA

A retrospective study of 191 patients who underwent either [^{18}F]DCFPyL PET-CT or [^{68}Ga]Ga-PSMA-11 PET-CT with 25 patients undergoing sequential examination with both radiopharmaceuticals[121], reported that at PSA levels between 0.5-3.5 ng/ml, DRs were higher with [^{18}F]DCFPyL, whilst in the 25

patients examined with both radiopharmaceuticals, [^{18}F]DCFPyL detected additional lesions in all positive [^{68}Ga]Ga-PSMA-11 PET-CT scans.

A retrospective analysis of [^{18}F]PSMA-1007 PET-CT findings in a cohort of 102 patients post-RP (median PSA 0.87 ng/ml, range 0.2-13.6 ng/ml), which were compared with a clinically matched cohort of different patients, who underwent [^{68}Ga]Ga-PSMA-11 PET-CT (median PSA 0.91 ng/ml, range 0.18-30.0 ng/ml), reported a similar number of PSMA-avid lesions attributable to recurrent disease with both radiopharmaceuticals and identical overall per patient DRs of 80.4%[122]. However, [^{18}F]PSMA-1007 revealed almost 5 times more benign PSMA avid foci compared to [^{68}Ga]PSMA-11, mainly in ganglia, unspecified lymph nodes and bone lesions, the latter of which were mainly in the ribs as well as vertebral column and pelvis, and importantly, without CT correlate. An intra-individual comparison of [^{18}F]PSMA-1007 PET-CT with other PSMA radiopharmaceuticals in 27 patients, showed an improved confidence to interpret small loco-regional nodes adjacent to the urinary tract with [^{18}F]PSMA-1007 PET-CT due to its low urinary excretion[123] (**Figure 17**). However, similar to the Rauscher et al.[122], a high number of non-specific unrelated PSMA-avid marrow foci were demonstrated, which were without CT correlate or signal abnormality on subsequent contrast-enhanced MRI evaluation. Both these studies emphasise the need for sophisticated reader training in [^{18}F]PSMA-1007 PET-CT and the importance of considering the clinical context when reporting such studies.

CONCLUSION

PET-CT in CaP is superior to conventional imaging (CT and BS) both for staging and in BCR due to their high DRs at clinically relevant low PSA levels, with resultant significant impact on patient management. Novel PET radiopharmaceuticals continue to be developed[124] including [^{18}F]PSMA-11[125], [^{18}F]JK-PSMA-7[126], and most recently radiohybrid PSMA (rhPSMA) ligands, which are a new class of theranostic PSMA-targeting PET agent, which have shown promising initial data in the setting of BCR post-RP[127].

Despite the growing body of evidence demonstrating the superiority of ^{68}Ga- and ^{18}F-labelled PSMA PET radiopharmaceuticals, they remain without FDA, EMA or NICE approval. Nevertheless, PSMA PET-CT has been incorporated into the most recent iteration of the joint EAU-ESTRO-ESUR-SIOG guidelines on CaP[52], and is currently recommended for use in patients with persistent or newly raised PSA levels (> 0.2 ng/ml) post-RP, or in patients with PSA recurrence post-RT who are eligible for curative salvage surgery. PSMA PET-CT in staging is currently not recommended due to uncertainty regarding the clinical benefit of detecting extraprostatic sites of disease at such an early timepoint, and the optimal management of such patients, e.g. systemic therapy vs. primary tumour directed treatment in conjunction with metastasis-directed therapy. Randomised prospective clinical trials including the recently completed ProPSMA study[70], comparing management based on conventional imaging/non-PSMA PET-based radiopharmaceutical imaging vs. PSMA PET-CT guided treatment, for both staging and BCR, are required to provide information on comparative diagnostic accuracy, impact on management, and most importantly clinical outcomes. The emergence of such data will help establish PSMA PET-CT into routine clinical practice.

FIGURE LEGENDS

Figure 1: Normal biodistribution of FEC.

Physiological biodistribution of FEC on PET maximum intensity projection (MIP) (A) and sagittal PET (B). Note symmetrical low-grade uptake frequently demonstrated in small reactive intrathoracic nodes (solid back and white arrows) on coronal PET and fused PET-CT images (C&D).

Figure 2: Normal biodistribution of [^{18}F]Fluciclovine.

Physiological biodistribution of [^{18}F]Fluciclovine on PET MIP (A) and sagittal PET (B). Note the minimal urinary activity in the bladder (*) on axial PET and fused PET-CT images (C&D). *Images courtesy of Dr Eugene Teoh, Blue Earth Diagnostics Ltd, Oxford, UK.*

Figure 3: Normal biodistribution of [^{68}Ga]GaPSMA-11.

Physiological biodistribution of [^{68}Ga]Ga-PSMA-11 on PET MIP (A) and sagittal PET (B). Note low-grade uptake in the left cervical ganglion (dashed white arrows) and left coeliac ganglion (solid white arrows) on axial PET and fused PET-CT images (C&D and E&F), not to be misinterpreted as pathological nodal uptake.

Figure 4: Normal biodistribution of [^{68}Ga]Ga-THP-PSMA.

Physiological biodistribution of [^{68}Ga]Ga-THP-PSMA on PET MIP (A) and sagittal PET (B) with the intensity of physiological uptake, including prominent duodenal uptake, lower than that observed with [^{68}Ga]Ga-PSMA-11. Early dynamic axial CT and fused PET-CT images at 0-3 minutes (C&D), 3-7 minutes (E&F) and 7-10 minutes (G&H) enable assessment of the prostate bed prior to accumulation of intense urinary activity in the bladder on half body imaging (60 minutes p.i).

Figure 5: Normal biodistribution of [^{18}F]PSMA-1007.

Physiological biodistribution of [^{18}F]PSMA-1007 on PET MIP (A) and sagittal PET (B) in a similar biodistribution to [^{68}Ga]Ga-PSMA-11. Note the minimal urinary activity in the bladder (*) on axial CT and fused PET-CT images (C&D) and focal uptake in a left sacral ganglion (white arrowheads), coeliac ganglia (dashed white arrows) and cervical ganglia (solid white arrows) on axial CT and fused PET-CT images (E&F, G&H and I&J). *Images courtesy of GenesisCare, Oxford, UK.*

Figure 6: FEC PET-CT in staging of CaP.

GS 4 + 3 CaP, PSA 9.3ng/ml, T2aN0 on mpMRI. PET MIP (A) axial CT, PET and fused PET-CT images (B-D) demonstrate a choline avid (SUVmax 6.3) right basal prostatic tumour (*). Axial CT, PET and fused PET-CT images (E-G) demonstrate low-grade uptake (SUVmax 2.3) in non-enlarged right obturator and right internal iliac nodes (solid black and white arrows) and a similar sized, similar avidity (SUVmax 2.5) left obturator node (dashed black and white arrow); the right pelvic nodes were metastatic on histology, but there was no metastatic disease in the resected left pelvic nodes.

Figure 7: [^{18}F]Fluciclovine PET-CT in staging of CaP.

GS 4 + 5 CaP, PSA of 32ng/ml. PET MIP (A), axial CT and axial fused PET-CT images (B&C, D&E) demonstrate fluciclovine uptake in 2 sub-cm short axis diameter right internal and external iliac nodes (black and white solid arrows) and a similar sized, similar avidity left internal iliac node (black and white dashed arrows); these were confirmed metastatic on histology. Note the minimal urinary activity in the bladder (*) with [^{18}F]Fluciclovine. *Images courtesy of Professor David Schuster, Emory University, USA.*

Figure 8: [^{68}Ga]Ga-PSMA-11 PET-CT in staging of CaP.

GS 4 + 3 CaP, PSA 300 ng/ml, T3aN0M0 on mpMRI. Negative BS. PET MIP (A), axial CT and fused PET-CT images (B&C, D&E, F&G) demonstrate an intensely PSMA avid (SUVmax 37.1) bilateral prostatic

tumour (*) with a tiny PSMA avid (SUVmax 5.4) right internal iliac node (solid white arrow) and a small left femoral marrow metastasis (dashed white arrow).

Figure 9: [^{68}Ga]Ga-THP-PSMA PET-CT in staging of CaP.

GS 4 + 4 CaP, PSA 27.7ng/ml, T3bN0M0 on mpMRI. Negative BS. PET MIP (A), axial CT and fused PET-CT images (B&C) demonstrate high-grade uptake (SUVmax 12.5) in a predominantly left sided prostatic tumour (*) with low-grade uptake (SUVmax 1.6) in a 6 x 6mm left internal iliac node (black and white dashed arrows) on axial PET and fused PET-CT images (D&E), high-grade uptake (SUVmax 11.1) in a 14 x 14mm superior mesorectal node (solid black and white arrows) and a L2 vertebral body metastasis (black and white arrowheads) on axial CT and fused PET-CT images (F&G, H&I).

Figure 10: [^{18}F]PSMA-1007 PET-CT in staging of CaP.

GS 4 + 4 CaP, PSA 20 ng/ml, T3bN0M0 on mpMRI. Intensely PSMA avid (SUVmax 16.0) bilateral peripheral zone prostatic tumour (*) on PET MIP (A) and axial CT and fused PET-CT images (B&C) concordant with mpMRI sequences; axial T2-weighted (D), DCE-MR (E), DW (F) and apparent diffusion coefficient (G) imaging. Note symmetrical low-grade uptake in bilateral non-enlarged distal external iliac nodes presumed benign and reactive (solid black and white arrows) and heterogeneous rib uptake, e.g. right 2nd rib (dashed black and white arrows) without CT abnormality, on PET MIP (A), axial CT and fused PET-CT images (H&I, J&K), also presumed benign[122,123]. *Images courtesy of GenesisCare, Oxford, UK.*

Figure 11: [^{11}C]choline PET-CT in BCR.

GS 3 + 4 CaP, post-RP with left pelvic nodal dissection (pT3aN1M0) with PSA rise to 5.4ng/ml. PET MIP (A), axial CT and fused PET-CT images (B&C, D&E) demonstrate 2 choline avid left internal iliac nodes (solid black and white arrows) measuring 10 x 13mm (SUVmax 8.3) and 8 x 11mm (SUVmax 7.1). Note the minimal urinary activity in the bladder (*).

Figure 12: FEC PET-CT in BCR.

GS 4 + 5 CaP, post-RP and bilateral pelvic nodal dissection (pT3bN1M0) with positive resection margins and rapid PSA rise to 15ng/ml; staging CT only identified an old 'traumatic' fracture of the right pubic ramus. PET MIP (A), axial CT and fused PET-CT images (B&C, D&E, F&G, H&I) demonstrate multi-focal sites of choline avid recurrent disease including sclerotic right inferior pubic ramus (*) and CT occult left inferior pubic ramus (black and white arrowheads) bone metastases, and left hilar (solid black and white arrows) and left supraclavicular fossa nodal metastases (dashed black and white arrows).

Figure 13: [^{18}F]Fluciclovine PET-CT in BCR.

T3aN0M0 CaP, post-RT with rising PSA. PET MIP (A), axial CT and fused PET-CT images (B&C, D&E) demonstrate multiple, predominantly non-enlarged sub-cm short axis diameter retroperitoneal nodes (solid and dashed black and white arrows). Note the minimal urinary activity in the bladder (*). *Images courtesy of Dr Eugene Teoh, Blue Earth Diagnostics Ltd, Oxford, UK.*

Figure 14: [^{68}Ga]Ga-PSMA-11 PET-CT in BCR

GS 3 + 4 CaP, post-RP (pT2N0M0) with PSA rise to 3.7ng/ml. PET MIP (A), axial CT and fused PET-CT images (B&C, D&E) demonstrate an intensely PSMA avid (SUVmax 26.4) 4 x 6mm external iliac node (dashed black and white arrows) and moderately PSMA avid (SUVmax 7.3) 4 x 6mm left common iliac node (solid black and white arrows).

Figure 15: [^{68}Ga]Ga-THP-PSMA PET-CT in BCR.

GS 4 + 3 CaP, post-RP and left pelvic lymph node dissection (pT3bN1M0) with PSA rise to 1.4ng/ml. PET MIP (A), axial CT and fused PET-CT images (B&C, D&E) demonstrate low-grade PSMA uptake (SUVmax 4.1) in a 8 x 9mm left para-aortic node (dashed white arrows) and a similar sized, similar intensity aortocaval node (solid black and white arrows) in keeping with disease relapse.

Figure 16: [^{18}F]PSMA-1007 in BCR.

GS 4 + 5 CaP, post-RP with nodal dissection (pT3bN1M0) with PSA rise to 0.98ng/ml. PET MIP (A), axial CT and fused PET-CT images (B&C, D&E, F&G) demonstrate an intensely PSMA avid (SUVmax 63.4) 12 x 14mm nodule (black and white arrowheads) anterior to the bladder containing minimal urinary activity (*) and a PSMA avid (SUVmax 26.2) solitary sclerotic right iliac bone metastasis (solid black and white arrows). Note incidental PSMA avid (SUVmax 8.4) T5 vertebral Paget's disease (dashed white arrows) with heterogeneous sclerosis, cortical thickening and expansion on CT. *Images courtesy of GenesisCare, Oxford, UK.*

Figure 17: [^{18}F]PSMA-1007 in BCR

GS 4 + 3 CaP, post-RP with PSA rise to 4ng/ml. PET MIP (A), axial CT and fused PET-CT images (B&C, D&E) demonstrate PSMA avid local recurrence in the right prostatectomy bed (black and white arrowheads) not appreciable on CT, and only discernible on PET, due to the absence of significant urinary activity in the bladder. Axial CT and fused PET-CT images (F&G, H&I) demonstrate a 5 x 6mm PSMA avid (SUVmax 5.0) right obturator node (black and white dashed arrows) and a PSMA avid 5 x 7mm (SUVmax 8.3) right external iliac node (solid black and white arrows). Note the equivocal left iliac bone focus (*) without CT abnormality. *Images courtesy of GenesisCare, Oxford, UK.*

REFERENCES

1. National Prostate Cancer Audit Annual Report 2019. https://www.npca.org.uk/reports/npca-annual-report-2019/. Accessed February, 2020.

2. Cancer Research UK. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer. Accessed February 2020.

3. Zhang L, Tang M, Chen S, Lei X, Zhang X, Huan Y. A meta-analysis of use of prostate imaging reporting and data system version 2 (PI-RADS V2) with multiparametric MR imaging for the detection of prostate cancer. *Eur Radiol*. 2017;27:5204-5214.

4. Woo S, Suh CH, Kim SY, Cho JY, Kim SH. The diagnostic performance of MRI for detection of lymph node metastasis in bladder and prostate cancer: An updated systematic review and diagnostic meta-analysis. *Am J Roentgenol*. 2018;210:W95-W109.

5. Hovels AM, Heesakkers RA, Adang EM, et al. The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: A meta-analysis. *Clin Radiol*. 2008;63:387-395.

6. Suh CH, Shinagare AB, Westenfield AM, Ramaiya NH, Van den Abbeele, A D, Kim KW. Yield of bone scintigraphy for the detection of metastatic disease in treatment-naive prostate cancer: A systematic review and meta-analysis. *Clin Radiol*. 2018;73:158-167.

7. Beresford MJ, Gillatt D, Benson RJ, Ajithkumar T. A systematic review of the role of imaging before salvage radiotherapy for post-prostatectomy biochemical recurrence. *Clin Oncol* 2010;22:46-55.

8. Siva S, Udovicich C, Tran B, Zargar H, Murphy DG, Hofman MS. Expanding the role of small-molecule PSMA ligands beyond PET staging of prostate cancer. *Nat Rev Urol*. 2020;17:107-118.

9. Awwad HM, Geisel J, Obeid R. The role of choline in prostate cancer. *Clin Biochem*. 2012;45:1548-1553.

10. Muller SA, Holzapfel K, Seidl C, Treiber U, Krause BJ, Senekowitsch-Schmidtke R. Characterization of choline uptake in prostate cancer cells following bicalutamide and docetaxel treatment. *Eur J Nucl Med Mol Imaging*. 2009;36:1434-1442.

11. Yoshimoto M, Waki A, Obata A, Furukawa T, Yonekura Y, Fujibayashi Y. Radiolabeled choline as a proliferation marker: Comparison with radiolabeled acetate. *Nucl Med Biol*. 2004;31:859-865.

12. Breeuwsma AJ, Pruim J, Jongen MM, et al. In vivo uptake of [^{11}C]choline does not correlate with cell proliferation in human prostate cancer. *Eur J Nucl Med Mol Imaging*. 2005;32:668-673.

13. Hara T, Kosaka N, Kishi H. PET imaging of prostate cancer using carbon-11-choline. *J Nucl Med*. 1998;39:990-995.

14. von Eyben FE, Kairemo K. Meta-analysis of ^{11}C-choline and ^{18}F-choline PET/CT for management of patients with prostate cancer. *Nucl Med Commun*. 2014;35:221-230.

15. Evangelista L, Cervino AR, Guttilla A, Zattoni F, Cuccurullo V, Mansi L. ^{18}F-fluoromethylcholine or ^{18}F-fluoroethylcholine pet for prostate cancer imaging: Which is better? A literature revision. *Nucl Med Biol*. 2015;42:340-348.

16. Frood R, Baren J, McDermott G, Bottomley D, Patel C, Scarsbrook A. Diagnostic performance of a streamlined ^{18}F-choline PET-CT protocol for the detection of prostate carcinoma recurrence in combination with appropriate-use criteria. *Clin Radiol*. 2018;73:632-639.

17. Fabbri C, Galassi R, Moretti A, et al. Radiation dosimetry of ^{18}F-fluorocholine PET/CT studies in prostate cancer patients. *Phys Med*. 2014;30:346-351.

18. Shoup TM, Olson J, Hoffman JM, et al. Synthesis and evaluation of [^{18}F]1-amino-3-fluorocyclobutane-1-carboxylic acid to image brain tumors. *J Nucl Med*. 1999;40:331-338.

19. Schuster DM, Nye JA, Nieh PT, et al. Initial experience with the radiotracer anti-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid (anti-[^{18}F]FACBC) with PET in renal carcinoma. *Mol Imaging Biol*. 2009;11:434-438.

20. Okudaira H, Shikano N, Nishii R, et al. Putative transport mechanism and intracellular fate of trans-1-amino-3-^{18}F-fluorocyclobutanecarboxylic acid in human prostate cancer. *J Nucl Med*. 2011;52:822-829.

21. Segawa A, Nagamori S, Kanai Y, Masawa N, Oyama T. L-type amino acid transporter 1 expression is highly correlated with gleason score in prostate cancer. *Mol Clin Oncol*. 2013;1:274-280.

22. Schuster DM, Nanni C, Fanti S, et al. Anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid: Physiologic uptake patterns, incidental findings, and variants that may simulate disease. *J Nucl Med*. 2014;55:1986-1992.

23. Nye JA, Schuster DM, Yu W, Camp VM, Goodman MM, Votaw JR. Biodistribution and radiation dosimetry of the synthetic nonmetabolized amino acid analogue anti-^{18}F-FACBC in humans. *J Nucl Med*. 2007;48:1017-1020.

24. Gordon IO, Tretiakova MS, Noffsinger AE, Hart J, Reuter VE, Al-Ahmadie HA. Prostate-specific membrane antigen expression in regeneration and repair. *Mod Pathol*. 2008;21:1421-1427.

25. Silver DA, Pellicer I, Fair WR, Heston WD, Cordon-Cardo C. Prostate-specific membrane antigen expression in normal and malignant human tissues. *Clin Cancer Res*. 1997;3:81-85.

26. Foss CA, Mease RC, Cho SY, Kim HJ, Pomper MG. GCPII imaging and cancer. *Curr Med Chem*. 2012;19:1346-1359.

27. Marchal C, Redondo M, Padilla M, et al. Expression of prostate specific membrane antigen (PSMA) in prostatic adenocarcinoma and prostatic intraepithelial neoplasia. *Histol Histopathol*. 2004;19:715-718.

28. Bostwick DG, Pacelli A, Blute M, Roche P, Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: A study of 184 cases. *Cancer*. 1998;82:2256-2261.

29. Troyer JK, Beckett ML, Wright GL. Location of prostate-specific membrane antigen in the LNCaP prostate carcinoma cell line. *Prostate*. 1997;30:232-242.

30. Haseman MK, Rosenthal SA, Polascik TJ. Capromab pendetide imaging of prostate cancer. *Cancer Biother Radiopharm*. 2000;15:131-140.

31. Maurer T, Eiber M, Schwaiger M, Gschwend JE. Current use of PSMA-PET in prostate cancer management. *Nat Rev Urol*. 2016;13:226-235.

32. Eder M, Schafer M, Bauder-Wust U, et al. ^{68}Ga-complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging. *Bioconjug Chem*. 2012;23:688-697.

33. Rischpler C, Beck TI, Okamoto S, et al. ^{68}Ga-PSMA-HBED-CC uptake in cervical, celiac, and sacral ganglia as an important pitfall in prostate cancer PET imaging. *J Nucl Med*. 2018;59:1406-1411.

34. Afshar-Oromieh A, Malcher A, Eder M, et al. PET imaging with a [^{68}Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: Biodistribution in humans and first evaluation of tumour lesions. *Eur J Nucl Med Mol Imaging*. 2013;40:486-495.

35. Afshar-Oromieh A, Sattler LP, Mier W, et al. The clinical impact of additional late PET/CT imaging with ^{68}Ga-PSMA-11 (HBED-CC) in the diagnosis of prostate cancer. *J Nucl Med*. 2017;58:750-755.

36. Hohberg M, Kobe C, Tager P, et al. Combined early and late [^{68}Ga]PSMA-HBED-CC PET scans improve lesion detectability in biochemical recurrence of prostate cancer with low PSA levels. *Mol Imaging Biol*. 2019;21:558-566.

37. Haupt F, Dijkstra L, Alberts I, et al. ^{68}Ga-PSMA-11 PET/CT in patients with recurrent prostate cancer-a modified protocol compared with the common protocol. *Eur J Nucl Med Mol Imaging*. 2020;47:624-631.

38. Afshar-Oromieh A, Hetzheim H, Kubler W, et al. Radiation dosimetry of ^{68}Ga-PSMA-11 (HBED-CC) and preliminary evaluation of optimal imaging timing. *Eur J Nucl Med Mol Imaging*. 2016;43:1611-1620.

39. Benesova M, Schafer M, Bauder-Wust U, et al. Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. *J Nucl Med*. 2015;56:914-920.

40. Weineisen M, Schottelius M, Simecek J, et al. ^{68}Ga- and ^{177}Lu-labeled PSMA I&T: Optimization of a PSMA-targeted theranostic concept and first proof-of-concept human studies. *J Nucl Med*. 2015;56:1169-1176.

41. Young JD, Abbate V, Imberti C, et al. ^{68}Ga-THP-PSMA: A PET imaging agent for prostate cancer offering rapid, room-temperature, 1-step kit-based radiolabeling. *J Nucl Med*. 2017;58:1270-1277.

42. Hofman MS, Eu P, Jackson P, et al. Cold kit for prostate-specific membrane antigen (PSMA) PET imaging: Phase 1 study of ^{68}Ga-tris(hydroxypyridinone)-PSMA PET/CT in patients with prostate cancer. *J Nucl Med*. 2018;59:625-631.

43. Derlin T, Schmuck S, Juhl C, et al. Imaging characteristics and first experience of [^{68}Ga]THP-PSMA, a novel probe for rapid kit-based Ga-68 labeling and PET imaging: Comparative analysis with [^{68}Ga]PSMA I&T. *Mol Imaging Biol*. 2018;20:650-658.

44. Kesch C, Kratochwil C, Mier W, Kopka K, Giesel FL. ^{68}Ga or ^{18}F for prostate cancer imaging? *J Nucl Med*. 2017;58:687-688.

45. Cho SY, Gage KL, Mease RC, et al. Biodistribution, tumor detection, and radiation dosimetry of ^{18}F-DCFBC, a low-molecular-weight inhibitor of prostate-specific membrane antigen, in patients with metastatic prostate cancer. *J Nucl Med*. 2012;53:1883-1891.

46. Szabo Z, Mena E, Rowe SP, et al. Initial evaluation of [^{18}F]DCFPyL for prostate-specific membrane antigen (PSMA)-targeted PET imaging of prostate cancer. *Mol Imaging Biol*. 2015;17:565-574.

47. Wondergem M, van der Zant, F M, Knol RJJ, Lazarenko SV, Pruim J, de Jong IJ. ^{18}F-DCFPyL PET/CT in the detection of prostate cancer at 60 and 120 minutes: Detection rate, image quality, activity kinetics, and biodistribution. *J Nucl Med*. 2017;58:1797-1804.

48. Giesel FL, Hadaschik B, Cardinale J, et al. F-18 labelled PSMA-1007: Biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. *Eur J Nucl Med Mol Imaging*. 2017;44:678-688.

49. Rahbar K, Afshar-Oromieh A, Bogemann M, et al. ^{18}F-PSMA-1007 PET/CT at 60 and 120 minutes in patients with prostate cancer: Biodistribution, tumour detection and activity kinetics. *Eur J Nucl Med Mol Imaging*. 2018;45:1329-1334.

50. Goldberg H, Ahmad AE, Chandrasekar T, et al. Comparison of MRI- and TRUS-informed prostate biopsy for prostate cancer diagnosis in biopsy-naive men: A systematic review and meta-analysis. *J Urol*. 2019 doi: 10.1097/JU.0000000000000595.

51. National Institute for Health and Care Excellence (2019) Prostate Cancer: Diagnosis and management NICE [NG131]. https://www.nice.org.uk/guidance/ng131. Accessed February, 2020.

52. EAU-ESTRO-ESUR-SIOG guidelines on prostate cancer. https://uroweb.org/guideline/prostate-cancer/. Accessed February 2020.

53. Evangelista L, Cimitan M, Zattoni F, Guttilla A, Zattoni F, Saladini G. Comparison between conventional imaging (abdominal-pelvic computed tomography and bone scan) and [^{18}F]choline positron emission tomography/computed tomography imaging for the initial staging of patients with intermediate- to high-risk prostate cancer: A retrospective analysis. *Scand J Urol*. 2015;49:345-353.

54. Nitsch S, Hakenberg OW, Heuschkel M, et al. Evaluation of prostate cancer with ^{11}C- and ^{18}F-choline PET/CT: Diagnosis and initial staging. *J Nucl Med*. 2016;57(Suppl 3):38S-42S.

55. Beheshti M, Imamovic L, Broinger G, et al. ^{18}F Choline PET/CT in the preoperative staging of prostate cancer in patients with intermediate or high risk of extracapsular disease: A prospective study of 130 patients. *Radiology*. 2010;254:925-933.

56. Poulsen MH, Bouchelouche K, Hoilund-Carlsen PF, et al. [^{18}F]fluoromethylcholine (FCH) positron emission tomography/computed tomography (PET/CT) for lymph node staging of prostate cancer: A prospective study of 210 patients. *BJU Int*. 2012;110:1666-1671.

57. Evangelista L, Guttilla A, Zattoni F, Muzzio PC, Zattoni F. Utility of choline positron emission tomography/computed tomography for lymph node involvement identification in intermediate- to high-risk prostate cancer: A systematic literature review and meta-analysis. *Eur Urol*. 2013;63:1040-1048.

58. Turkbey B, Mena E, Shih J, et al. Localized prostate cancer detection with ^{18}F FACBC PET/CT: Comparison with MR imaging and histopathologic analysis. *Radiology*. 2014;270:849-856.

59. Jambor I, Kuisma A, Kahkonen E, et al. Prospective evaluation of ^{18}F-FACBC PET/CT and PET/MRI versus multiparametric MRI in intermediate- to high-risk prostate cancer patients (FLUCIPRO trial). *Eur J Nucl Med Mol Imaging*. 2018;45:355-364.

60. Suzuki H, Jinnouchi S, Kaji Y, et al. Diagnostic performance of ^{18}F-fluciclovine PET/CT for regional lymph node metastases in patients with primary prostate cancer: A multicenter phase II clinical trial. *Jpn J Clin Oncol*. 2019;49:803-811.

61. Kim SJ, Lee SW. The role of ^{18}F-fluciclovine PET in the management of prostate cancer: A systematic review and meta-analysis. *Clin Radiol*. 2019;74:886-892.

62. Petersen LJ, Zacho HD. PSMA PET for primary lymph node staging of intermediate and high-risk prostate cancer: An expedited systematic review. *Cancer Imaging*. 2020;20:10-9.

63. Petersen LJ, Nielsen JB, Langkilde NC, et al. ^{68}Ga-PSMA PET/CT compared with MRI/CT and diffusion-weighted MRI for primary lymph node staging prior to definitive radiotherapy in prostate cancer: A prospective diagnostic test accuracy study. *World J Urol*. 2019. doi: 10.1007/s00345-019-02846-z.

64. Lengana T, Lawal IO, Boshomane TG, et al. ^{68}Ga-PSMA PET/CT replacing bone scan in the initial staging of skeletal metastasis in prostate cancer: A fait accompli? *Clin Genitourin Cancer*. 2018;16:392-401.

65. Yaxley JW, Raveenthiran S, Nouhaud FX, et al. Outcomes of primary lymph node staging of intermediate and high risk prostate cancer with ^{68}Ga-PSMA positron emission tomography/computerized tomography compared to histological correlation of pelvic lymph node pathology. *J Urol*. 2019;201:815-820.

66. Luiting HB, van Leeuwen PJ, Busstra MB, et al. Use of gallium-68 prostate-specific membrane antigen positron-emission tomography for detecting lymph node metastases in primary and recurrent prostate cancer and location of recurrence after radical prostatectomy: An overview of the current literature. *BJU Int*. 2020;125:206-214.

67. Koschel S, Murphy DG, Hofman MS, Wong LM. The role of prostate-specific membrane antigen PET/computed tomography in primary staging of prostate cancer. *Curr Opin Urol*. 2019;29:569-577.

68. Roach PJ, Francis R, Emmett L, et al. The impact of ^{68}Ga-PSMA PET/CT on management intent in prostate cancer: Results of an australian prospective multicenter study. *J Nucl Med*. 2018;59:82-88.

69. Kulkarni M, Hughes S, Mallia A, et al. The management impact of ^{68}Gallium-tris(hydroxypyridinone) prostate-specific membrane antigen (^{68}Ga-THP-PSMA) PET-CT imaging for high-risk and biochemically recurrent prostate cancer. *Eur J Nucl Med Mol Imaging*. 2020;47:674-686.

70. Hofman MS, Murphy DG, Williams SG, et al. A prospective randomized multicentre study of the impact of gallium-68 prostate-specific membrane antigen (PSMA) PET/CT imaging for staging high-risk prostate cancer prior to curative-intent surgery or radiotherapy (proPSMA study): Clinical trial protocol. *BJU Int*. 2018;122:783-793.

71. Rowe SP, Gage KL, Faraj SF, et al. ^{18}F-DCFBC PET/CT for PSMA-based detection and characterization of primary prostate cancer. *J Nucl Med*. 2015;56:1003-1010.

72. Turkbey B, Mena E, Lindenberg L, et al. ^{18}F-DCFBC prostate-specific membrane antigen-targeted PET/CT imaging in localized prostate cancer: Correlation with multiparametric MRI and histopathology. *Clin Nucl Med*. 2017;42:735-740.

73. Gorin MA, Rowe SP, Patel HD, et al. Prostate specific membrane antigen targeted ^{18}F-DCFPyL positron emission tomography/computerized tomography for the preoperative staging of high risk prostate cancer: Results of a prospective, phase II, single center study. *J Urol*. 2018;199:126-132.

74. Schwenck J, Rempp H, Reischl G, et al. Comparison of ^{68}Ga-labelled PSMA-11 and ^{11}C-choline in the detection of prostate cancer metastases by PET/CT. *Eur J Nucl Med Mol Imaging*. 2017;44:92-101.

75. Giesel FL, Will L, Lawal I, et al. Intraindividual comparison of ^{18}F-PSMA-1007 and ^{18}F-DCFPyL PET/CT in the prospective evaluation of patients with newly diagnosed prostate carcinoma: A pilot study. *J Nucl Med*. 2018;59:1076-1080.

76. Stephenson AJ, Kattan MW, Eastham JA, et al. Defining biochemical recurrence of prostate cancer after radical prostatectomy: A proposal for a standardized definition. *J Clin Oncol*. 2006;24:3973-3978.

77. Roach M, Hanks G, Thames H, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO phoenix consensus conference. *Int J Radiat Oncol Biol Phys*. 2006;65:965-974.

78. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA*. 1999;281:1591-1597.

79. Van den Broeck T, van den Bergh, R C N, Arfi N, et al. Prognostic value of biochemical recurrence following treatment with curative intent for prostate cancer: A systematic review. *Eur Urol*. 2019;75:967-987.

80. King CR. The timing of salvage radiotherapy after radical prostatectomy: A systematic review. *Int J Radiat Oncol Biol Phys*. 2012;84:104-111.

81. Kawanaka Y, Kitajima KD, Yamamoto S, et al. Comparison of 11C-choline positron emission tomography/computed tomography (PET/CT) and conventional imaging for detection of recurrent prostate cancer. *Cureus*. 2018;10(7):e2966.

82. McCarthy M, Siew T, Campbell A, et al. ^{18}F-fluoromethylcholine (FCH) PET imaging in patients with castration-resistant prostate cancer: Prospective comparison with standard imaging. *Eur J Nucl Med Mol Imaging*. 2011;3Ω:14-22.

83. Fanti S, Minozzi S, Castellucci P, et al. PET/CT with ^{11}C-choline for evaluation of prostate cancer patients with biochemical recurrence: Meta-analysis and critical review of available data. *Eur J Nucl Med Mol Imaging*. 2016;43:55-69.

84. Evangelista L, Zattoni F, Guttilla A, et al. Choline PET or PET/CT and biochemical relapse of prostate cancer: A systematic review and meta-analysis. *Clin Nucl Med*. 2013;38:305-314.

85. Umbehr MH, Muntener M, Hany T, Sulser T, Bachmann LM. The role of 11C-choline and 18F-fluorocholine positron emission tomography (PET) and PET/CT in prostate cancer: A systematic review and meta-analysis. *Eur Urol*. 2013;64:106-117.

86. Vickers AJ, Brewster SF. PSA velocity and doubling time in diagnosis and prognosis of prostate cancer. *Br J Med Surg Urol*. 2012;5:162-168.

87. De Visschere, P J L, Standaert C, Futterer JJ, et al. A systematic review on the role of imaging in early recurrent prostate cancer. *Eur Urol Oncol*. 2019;2:47-76.

88. Treglia G, Ceriani L, Sadeghi R, Giovacchini G, Giovanella L. Relationship between prostate-specific antigen kinetics and detection rate of radiolabelled choline PET/CT in restaging prostate cancer patients: A meta-analysis. *Clin Chem Lab Med*. 2014;52:725-733.

89. Gillebert Q, Huchet V, Rousseau C, et al. ^{18}F-fluorocholine PET/CT in patients with occult biochemical recurrence of prostate cancer: Detection rate, impact on management and adequacy of impact. A prospective multicentre study. *PLoS One*. 2018;13:e0191487.

90. Ceci F, Herrmann K, Castellucci P, et al. Impact of ^{11}C-choline PET/CT on clinical decision making in recurrent prostate cancer: Results from a retrospective two-centre trial. *Eur J Nucl Med Mol Imaging*. 2014;41:2222-2231.

91. Schuster DM, Nieh PT, Jani AB, et al. Anti-3-[^{18}F]FACBC positron emission tomography-computerized tomography and ^{111}in-capromab pendetide single photon emission computerized tomography-computerized tomography for recurrent prostate carcinoma: Results of a prospective clinical trial. *J Urol*. 2014;191:1446-1453.

92. Odewole OA, Tade FI, Nieh PT, et al. Recurrent prostate cancer detection with anti-3-[^{18}F]FACBC PET/CT: Comparison with CT. *Eur J Nucl Med Mol Imaging*. 2016;43:1773-1783.

93. Nanni C, Zanoni L, Pultrone C, et al. ^{18}F-FACBC (anti1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid) versus ^{11}C-choline PET/CT in prostate cancer relapse: Results of a prospective trial. *Eur J Nucl Med Mol Imaging*. 2016;43:1601-1610.

94. Ren J, Yuan L, Wen G, Yang J. The value of anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid PET/CT in the diagnosis of recurrent prostate carcinoma: A meta-analysis. *Acta Radiol*. 2016;57:487-493.

95. Bach-Gansmo T, Nanni C, Nieh PT, et al. Multisite experience of the safety, detection rate and diagnostic performance of fluciclovine (^{18}F) positron emission tomography/computerized tomography imaging in the staging of biochemically recurrent prostate cancer. *J Urol*. 2017;197:676-683.

96. Andriole GL, Kostakoglu L, Chau A, et al. The impact of positron emission tomography with ^{18}F-fluciclovine on the treatment of biochemical recurrence of prostate cancer: Results from the LOCATE trial. *J Urol*. 2019;201:322-331.

97. Scarsbrook AF, Bottomley D, Teoh EJ, et al. Impact of ^{18}F-fluciclovine positron emission tomography on the management of patients with recurrence of prostate cancer: Results from the FALCON trial. *Int J Radiat Oncol Biol Phys*. 2020. doi: 10.1016/j.ijrobp.2020.01.050.

98. Giesel FL, Fiedler H, Stefanova M, et al. PSMA PET/CT with glu-urea-lys-(ahx)-[^{68}Ga(HBED-CC)] versus 3D CT volumetric lymph node assessment in recurrent prostate cancer. *Eur J Nucl Med Mol Imaging*. 2015;42:1794-1800.

99. Rauscher I, Maurer T, Beer AJ, et al. Value of ^{68}Ga-PSMA HBED-CC PET for the assessment of lymph node metastases in prostate cancer patients with biochemical recurrence: Comparison with histopathology after salvage lymphadenectomy. *J Nucl Med*. 2016;57:1713-1719.

100. Grubmuller B, Baltzer P, D'Andrea D, et al. ^{68}Ga-PSMA 11 ligand PET imaging in patients with biochemical recurrence after radical prostatectomy - diagnostic performance and impact on therapeutic decision-making. *Eur J Nucl Med Mol Imaging*. 2018;45:235-242.

101. Perera M, Papa N, Roberts M, et al. Gallium-68 prostate-specific membrane antigen positron emission tomography in advanced prostate cancer-updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: A systematic review and meta-analysis. *Eur Urol*. 2019. doi: 10.1016/j.eururo.2019.01.049.

102. Hope TA, Goodman JZ, Allen IE, Calais J, Fendler WP, Carroll PR. Metaanalysis of ^{68}Ga-PSMA-11 PET accuracy for the detection of prostate cancer validated by histopathology. *J Nucl Med*. 2019;60:786-793.

103. Pereira Mestre R, Treglia G, Ferrari M, et al. Correlation between PSA kinetics and PSMA-PET in prostate cancer restaging: A meta-analysis. *Eur J Clin Invest*. 2019;49:e13063.

104. Fendler WP, Calais J, Eiber M, et al. Assessment of ^{68G}a-PSMA-11 PET accuracy in localizing recurrent prostate cancer: A prospective single-arm clinical trial. *JAMA Oncol*. 2019;5:856-863.

105. Caroli P, Sandler I, Matteucci F, et al. ^{68}Ga-PSMA PET/CT in patients with recurrent prostate cancer after radical treatment: Prospective results in 314 patients. *Eur J Nucl Med Mol Imaging*. 2018;45:2035-2044.

106. Ekmekcioglu O, Busstra M, Klass ND, Verzijlbergen F. Bridging the imaging gap: PSMA PET/CT has a high impact on treatment planning in prostate cancer patients with biochemical recurrence - A narrative review of the literature. *J Nucl Med*. 2019;60:1394-1398.

107. Berliner C, Tienken M, Frenzel T, et al. Detection rate of PET/CT in patients with biochemical relapse of prostate cancer using [^{68}Ga]PSMA I&T and comparison with published data of [^{68}Ga]PSMA HBED-CC. *Eur J Nucl Med Mol Imaging*. 2017;44:670-677.

108. Derlin T, Schmuck S, Juhl C, et al. PSA-stratified detection rates for [^{68}Ga]THP-PSMA, a novel probe for rapid kit-based ^{68}Ga-labeling and PET imaging, in patients with biochemical recurrence after primary therapy for prostate cancer. *Eur J Nucl Med Mol Imaging*. 2018;45:913-922.

109. Treglia G, Annunziata S, Pizzuto DA, Giovanella L, Prior JO, Ceriani L. Detection rate of ^{18}F-labeled PSMA PET/CT in biochemical recurrent prostate cancer: A systematic review and a meta-analysis. *Cancers (Basel)*. 2019;11:710.

110. Mena E, Lindenberg ML, Shih JH, et al. Clinical impact of PSMA-based ^{18}F-DCFBC PET/CT imaging in patients with biochemically recurrent prostate cancer after primary local therapy. *Eur J Nucl Med Mol Imaging*. 2018;45:4-11.

111. Rousseau E, Wilson D, Lacroix-Poisson F, et al. A prospective study on ^{18}F-DCFPyL PSMA PET/CT imaging in biochemical recurrence of prostate cancer. *J Nucl Med*. 2019;60:1587-1593.

112. Mena E, Lindenberg ML, Turkbey IB, et al. ^{18}F-DCFPyL PET/CT imaging in patients with biochemical recurrence prostate cancer after primary local therapy. *J Nucl Med*. 2019. doi:10.2967/jnumed.119.234799.

113. Witkowska-Patena E, Gizewska A, Dziuk M, Misko J, Budzynska A, Walecka-Mazur A. Diagnostic performance of 18F-PSMA-1007 PET/CT in biochemically relapsed patients with prostate cancer with PSA levels ≤ 2.0 ng/ml. *Prostate Cancer Prostatic Dis*. 2019. doi: 10.1038/s41391-019-0194-6.

114. Giesel FL, Knorr K, Spohn F, et al. Detection efficacy of ^{18}F-PSMA-1007 PET/CT in 251 patients with biochemical recurrence of prostate cancer after radical prostatectomy. *J Nucl Med*. 2019;60:362-368.

115. Morigi JJ, Stricker PD, van Leeuwen PJ, et al. Prospective comparison of ^{18}F-fluoromethylcholine versus ^{68}Ga-PSMA PET/CT in prostate cancer patients who have rising PSA after curative treatment and are being considered for targeted therapy. *J Nucl Med*. 2015;56:1185-1190.

116. Alonso O, Dos Santos G, Garcia Fontes M, Balter H, Engler H. ^{68}Ga-PSMA and ^{11}C-choline comparison using a tri-modality PET/CT-MRI (3.0 T) system with a dedicated shuttle. *Eur J Hybrid Imaging*. 2018;2:9-1.

117. Witkowska-Patena E, Gizewska A, Dziuk M, Misko J, Budzynska A, Walecka-Mazur A. Head-to-head comparison of ^{18}F-prostate-specific membrane antigen-1007 and ^{18}F-fluorocholine PET/CT in biochemically relapsed prostate cancer. *Clin Nucl Med*. 2019;44:e629-e633.

118. Treglia G, Pereira Mestre R, Ferrari M, et al. Radiolabelled choline versus PSMA PET/CT in prostate cancer restaging: A meta-analysis. *Am J Nucl Med Mol Imaging*. 2019;9:127-139.

119. Calais J, Ceci F, Eiber M, et al. ^{18}F-fluciclovine PET-CT and ^{68}Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: A prospective, single-centre, single-arm, comparative imaging trial. *Lancet Oncol*. 2019;20:1286-1294.

120. Pernthaler B, Kulnik R, Gstettner C, Salamon S, Aigner RM, Kvaternik H. A prospective head-to-head comparison of ^{18}F-fluciclovine with ^{68}Ga-PSMA-11 in biochemical recurrence of prostate cancer in PET/CT. *Clin Nucl Med*. 2019;44:e566-e573.

121. Dietlein F, Kobe C, Neubauer S, et al. PSA-stratified performance of ^{18}F- and ^{68}Ga-PSMA PET in patients with biochemical recurrence of prostate cancer. *J Nucl Med*. 2017;58:947-952.

122. Rauscher I, Kronke M, Konig M, et al. Matched-pair comparison of ^{68}Ga-PSMA-11 PET/CT and ^{18}F-PSMA-1007 PET/CT: Frequency of pitfalls and detection efficacy in biochemical recurrence after radical prostatectomy. *J Nucl Med*. 2020;61:51-57.

123. Dietlein F, Kobe C, Hohberg M, et al. Intraindividual comparison of ^{18}F-PSMA-1007 with renally excreted PSMA ligands for PSMA-PET imaging in patients with relapsed prostate cancer. *J Nucl Med*. 2019. doi: 102967/jnumed.119.234898.

124. Mena E, Lindenberg LM, Choyke PL. New targets for PET molecular imaging of prostate cancer. *Semin Nucl Med*. 2019;49:326-336.

125. Piron S, De Man K, Van Laeken N, et al. Radiation dosimetry and biodistribution of ^{18}F-PSMA-11 for PET imaging of prostate cancer. *J Nucl Med*. 2019;60:1736-1742.

126. Dietlein F, Hohberg M, Kobe C, et al. An ^{18}F-labeled PSMA ligand for PET/CT imaging of prostate cancer patients: First-in-man observational study and clinical experience with ^{18}F-JK-PSMA-7 during the first year of application. *J Nucl Med*. 2020;61:202-209.

127. Eiber M, Kronke M, Wurzer A, et al. ^{18}F-rhPSMA-7 positron emission tomography for the detection of biochemical recurrence of prostate cancer following radical prostatectomy. *J Nucl Med*. 2019. doi: 10.2967/jnumed.119.234914.